CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-253

NAME OF APPLICANT / NDA HOLDER
Schwarz Biosciences, Inc.
(wholly-owned subsidiary of Schwarz Pharma AG)

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)	STRENGTH(S)
LACOSAMIDE	50, 100, 150, 200, 250 & 300 mg film-coated tablets

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
U.S. Re-Issue Patent # 38,551	07/06/2004	03/17/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
Research Corporation Technologies, Inc.	101 North Wilmot Road - Suite 600	
	City/State: Tucson, AZ	
	ZIP Code: 85711	FAX Number *(if available)*
	Telephone Number: (520) 748-4400	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☑ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**

The patent claims the form of the drug substance described in the pending application, among others, and is submitted for listing on that basis. Accordingly, no further testing is required.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
4.2 Claim Number (*as listed in the patent*) Claims 11-13	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☑ Yes ☐ No	

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*

Treatment of partial-onset seizures as adjunctive therapy in patients with epilepsy aged 16 years and older in accordance with proposed labeling, including for example the Indications and Usage, Dosage and Administration, and Clinical Trials sections.

Management of neuropathic pain associated with diabetic peripheral neuropathy and/or [redacted] in accordance with proposed labeling, including for example the Indications and Usage, Dosage and Administrative, and Clinical Trials sections.

b(4)

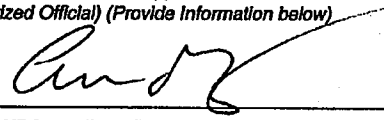
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/21/07

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Alan Blumberg, Sr. Director, Regulatory Affairs, Schwarz Biosciences, Inc., (wholly-owned subsidiary of Schwarz Pharma AG)	
Address P.O. Box 110167	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number (919) 767-2513
FAX Number *(if available)* (919) 767-3139	E-Mail Address *(if available)* alan.blumberg@ucb-group.com

Department of Health and Human Services
Food and Drug Administration

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TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)	STRENGTH(S)
LACOSAMIDE	10 mg/mL injection

DOSAGE FORM
Injection

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1. GENERAL

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U.S. Re-issue Patent # 38,551	07/06/2004	03/17/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
Research Corporation Technologies, Inc.	101 North Wilmot Road - Suite 600	
	City/State: Tucson, AZ	
	ZIP Code: 85711	FAX Number *(if available)*
	Telephone Number: (520) 748-4400	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☐ Yes	☑ No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

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2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
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2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**

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2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No

4.2 Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
Claims 11-13	☑ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of partial-onset seizures as adjunctive therapy in patients with epilepsy aged 16 years and older in accordance with proposed labeling, including for example the Indications and Usage, Dosage and Administration, and Clinical Trials sections.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

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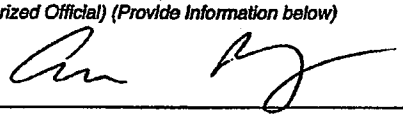	9/21/07

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Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Alan Blumberg, Sr. Director, Regulatory Affairs, Schwarz Biosciences, Inc., (wholly-owned subsidiary of Schwarz Pharma AG)

Address	City/State
P.O. Box 110167	Research Triangle Park, NC
ZIP Code	**Telephone Number**
27709	(919) 767-2513
FAX Number *(if available)*	**E-Mail Address *(if available)***
(919) 767-3139	alan.blumberg@ucb-group.com

EXCLUSIVITY SUMMARY

NDA # 22-253 & 22-254 SUPPL # HFD # 120

Trade Name Vimpat Tablets & Injection

Generic Name lacosamide

Applicant Name Schwarz Biosciences, Inc.

Approval Date, If Known 10/28/08

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) original NDAs

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Jacqueline H. Ware, PharmD
Title: Supervisory Regulatory Health Project Manager
Date: 11/18/08

Name of Office/Division Director signing form: Russell Katz, M.D.
Title: Director, Division of Neurology Products, ODE1, CDER

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
11/21/2008 07:53:34 AM

1 EXCLUSIVITY REQUEST

In accordance with 21 C.F.R § 314.50(j), Schwarz claims five years of new chemical entity exclusivity under 21 C.F.R § 314.108(b)(2) for lacosamide, the active moiety that is the subject of NDAs 22,253; 22,254; and 22,255.

Schwarz requests five years of marketing exclusivity for lacosamide, and, pursuant to 21 C.F.R § 314.50(j)(3), certifies that, to the best of the company's knowledge, no drug product containing lacosamide has previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-253; 22-254 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:Division of Neurology Products PDUFA Goal Date: 10/28/08 Stamp Date: 9/25/07

Proprietary Name: Vimpat

Established/Generic Name: Lacosamide

Dosage Form: Tablets & Injection

Applicant/Sponsor: Schwarz Bioscience

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Adjunctive treatment of partial onset seizures

Q1: Is this application in response to a PREA PMC/PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC/PMR #:_____

Does the division agree that this is a complete response to the PMC/PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

- ☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☒ Deferred for some or all pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☒	Neonate	__ wk. 0 mo.	__ wk. 1 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☒ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	__ yr. 1 mo.	16 yr. 11 mo.	☒	☒	☐	☒
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): July 31, 2013						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Jackie Ware, Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jackie Ware
11/19/2008 08:51:27 AM

DEBARMENT CERTIFICATION

SCHWARZ BIOSCIENCES, INC. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Richard Todd 9 Aug 2007

Signature/Date

Richard Todd

Associate Director

R&D Quality Management

SCHWARZ BIOSCIENCES, INC.

Ware, Jacqueline H

From: Blumberg Alan [Alan.Blumberg@ucb-group.com]
Sent: Tuesday, October 28, 2008 2:23 PM
To: Ware, Jacqueline H
Subject: Post-approval Commitments NDA 22-253 and 22-254
Importance: High
Attachments: emfalert.txt

Dear Jackie,

Please reference your emails to me dated, October 23, 2008 and October 24, 2008 whereby FDA requested that UCB conduct the following investigations:

- A nonclinical study in rats to examine the effects of lacosamide on brain development during the prenatal and early postnatal periods using more sensitive techniques for assessing CNS structure and function than were employed in the standard pre- and postnatal development study. You should consider the use of multiple daily dosing as a means of achieving higher plasma drug exposures during pregnancy and to better mimic the human exposure pattern.
- *In vitro* data to determine which enzymes may be involved in the metabolism of lacosamide in addition to CYP2C19.

UCB hereby commits to submitting to FDA a protocol for each study within 6 months of the approval date. Furthermore, UCB additionally commits to provide FDA with final study reports for the pre-/postnatal study within 30 months of the approval of lacosamide and for the in vitro metabolism study within 18 months of the approval of lacosamide. We understand that timeline to the final study reports may be revisited should circumstances warrant.

Also in the October 23, 2008 email, FDA provided comments from CDER's Division of Medication Error Prevention and to agree to certain changes to the carton and container labeling. **UCB agrees to address the comments and make the requested changes to the carton and container labeling.**

In the October 24, 2008 email FDA additionally provided carton and container comments. **UCB agrees to address the comments and make the requested changes to the carton and container labeling.**

Best regards,

Alan

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Thursday, October 23, 2008 11:55 AM
To: 'Blumberg Alan'
Cc: Ware, Jacqueline H
Subject: FDA Request - NDA 22-253 and 22-254

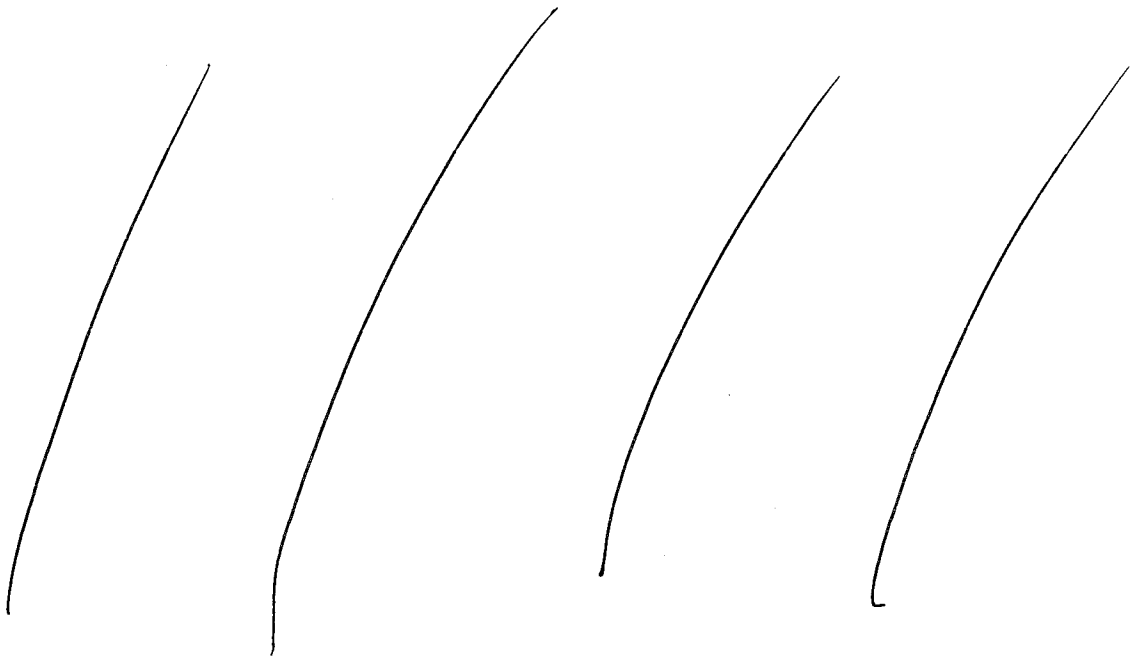
Dear Alan,
The Division requests that UCB agree conduct the following investigations post-approval and provide a reasonable timeframe for submission of the respective final study reports.

- A nonclinical study in rats to examine the effects of lacosamide on brain development during the prenatal and early postnatal periods using more sensitive techniques for assessing CNS structure and function than were employed in the standard pre- and postnatal development study. You should consider the use of multiple daily dosing as a means of achieving higher plasma drug exposures during pregnancy and to better mimic the human exposure pattern.

- *In vitro* data to determine which enzymes may be involved in the metabolism of lacosamide in addition to CYP2C19.

In addition, we ask that you address the following comments from CDER"s Division of Medication Error Prevention and agree to make the following changes to the lacosamide carton & container labeling :

b(4)



g

If you have any questions about the above, please let me know.

Thank you,
Jackie

****
Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Supervisory Regulatory Project Manager

Division of Neurology Products
Center for Drug Evaluation and Research, FDA

10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
: 301-796-9842
ail: jacqueline.ware@fda.hhs.gov

Keefe, Stephanie

From: Heimann, Martha R
Sent: Tuesday, October 21, 2008 4:46 PM
To: Keefe, Stephanie
Subject: RE: Lacosamide question

Stephanie-

We did not request that methods validation (testing by an FDA lab) be done for any of the lacosamide NDAs so there isn't anything that needs to go into the package. I've also told Jackie that the methods validation paragraph does not need to be included in the action letter.

Thanks,
Martha

From: Keefe, Stephanie
Sent: Tuesday, October 21, 2008 4:37 PM
To: Heimann, Martha R
Subject: Lacosamide question

Martha,

I am currently working on an Action package for Jackie, for Lacosamide. Could you please let me know if a "Methods Validation" document was entered into DFS for this NDA series? Or is it not finalized yet? If it is in DARRTS, can you send me the pdf version? I may have it already but it may be titled differently.

Thanks for your help!!

~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Stephanie N. Keefe
Consumer Safety Officer (CSO)
Division of Neurology Products
Food and Drug Administration (FDA)
Phone: 301-796-4098
~~~~~~~~~~~~~~~~~~~~~~~~~~~~

Keefe, Stephanie

From: Gunther, Sheryl
Sent: Monday, October 20, 2008 5:36 PM
To: Keefe, Stephanie
Subject: RE: Lacosamide Inquiry

Attachments: ClinicalInspectionSummary.pdf

Hi Stephanie:

I have attached the final clinical inspection summary for Lacosamide. This document is saved in DFS, as is the NAI letter to Dr. Krauss mentioned in your email below. The letters to other investigators have not been finalized yet, however.

Please let me know if there is anything else I can provide. I am currently on maternity leave, as my son was born last week. I will check my email, however.

Thanks,
Sheryl

ClinicalInspectionSummary.pdf ...

From: Keefe, Stephanie
Sent: Monday, October 20, 2008 3:32 PM
To: Gunther, Sheryl
Subject: Lacosamide Inquiry

Sheryl,

I am in the process of composing an Action Package for Lacosamide NDA's 22-253, -254, — , was wondering if you had a Final Memo prepared, regarding the DSI Inspection Review Summary as well as all letters to investigators? I checked DFS and the only entries I have are the DSI Consult Request (electronically signed by J. Ware on 1/2/08) and an NAI letter (electronically signed by C. Lewin on 5/12/08) to one investigator. If you could send those attachments to me by COB Tuesday, that would be much appreciated.

b(4)

Thanks

~~~~~~~~~~~~~~~~~~~~~~~~~~~~

Stephanie N. Keefe
Consumer Safety Officer (CSO)
Division of Neurology Products
Food and Drug Administration (FDA)
Phone: 301-796-4098
~~~~~~~~~~~~~~~~~~~~~~~~~~~~

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

b(4)

NDA 22-253 Tablets
NDA 22-254 Injection

Schwarz Biosciences, Inc.
Attention: Alan Blumberg, Ph.D.
Senior Director, Regulatory Affairs
P.O.Box 110167
Research Triangle Park, NC 27709

Dear Dr. Blumberg:

Please refer to your September 28, 2007 new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lacosamide Tablets, Injection

On July 14, 2008, we received your July 11, 2008 major amendments to these applications. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of these submissions. The extended user fee goal date is October 28, 2008.

If you have any questions, call Dr. Jacqueline H. Ware, Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph., M.S.
Supervisory Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robbin Nighswander
7/31/2008 01:17:05 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 25, 2008

TO: Russell G. Katz, M.D.
Director
Division of Neurology Products (DNP)

FROM: Hyojong Kwon, Ph.D.
Michael F. Skelly, Ph.D.
Xikui Chen, Ph.D.
Martin K. Yau, Ph.D.
Pharmacologists
Division of Scientific Investigations

Through: C.T. Viswanathan, Ph.D. CTV 7/25/08
Associate Director (Bioequivalence)
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-254, Vimpat (Lacosamide) Injection, 200 mg/20 mL, Sponsored by Schwarz Biosciences, Inc.

At the request of the DNP, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following studies:

Study# SP658: Randomized, open-label, single-dose, 3-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in 24 healthy male subjects

Study# SP645: Randomized, open-label, single-dose, 2-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in healthy male subjects

The clinical and analytical portions of study# SP658 were conducted at [redacted], and Schwarz Pharma AG, Monheim, Germany, respectively.

The clinical and analytical portions of the study# SP645 were conducted at [redacted]

[redacted] and [redacted] respectively. b(4)

Clinical Data Audits

Following the inspection at [redacted] (3/10-14/08) and [redacted] (3/10-14/08), Form FDA-483 was issued at each clinical site. The objectionable observations and our evaluation are provided below: b(4)

[redacted] ((Study# SP658) and [redacted] (Study# SP 645) b(4)

1. Samples of the test article and reference standard used in a bioequivalence study were not retained. Specifically, the test article SPM 927 10 mg/ml intravenous solution and the reference article SPM 927 100 mg tablet, used in the Bioequivalence Study conducted under application NDA 22-254, identified as Trial No. 645 and No. 658 were not retained at the clinical research organization sites as required under the regulation.

Both clinical sites (testing facilities) failed to randomly select and retain reserve samples of test and reference products, as required under 21 CFR 320.38. Therefore, the authenticity of the test and reference products used in Studies No. 645 and No. 658 cannot be assured. b(4)

[redacted] (Study# SP645)

2. Failure to identify the lot number of the SPM-solution used to make the intravenous (IV) test medication.

The raw data for preparation of the IV study medication does not identify the lot number. Thus, identity of the IV solution administered to study subjects cannot be confirmed.

3. Failure to define permitted activities for two of the staff members who were allowed to draw blood of the study subjects.

These two staff members with undefined work involvement with the study were allowed to draw blood samples from 9 subjects; although objectionable, no safety concern was apparent.

4. Failure to have 19% of the drug testing reports signed-off prior to administration of the study medication.

The study protocol required subjects to pass a drug test before admission to the study and to receive study medication. The clinical investigator failed to review the results for nine subjects (#24018, 24981, 91110, 26520, 11255 (on 5/13/03 and 5/20/03), 26626, 10061 (5/15/03 and 5/22/03) prior to dosing. Nonetheless, drug test results were included in Final Report Listing 9.3 (Alcohol and Drug Screening); the results of the nine subjects were not deemed clinically relevant.

Analytical Data Audits

Due to last minute competing priorities, the audit of the bioanalytical data was conducted remotely via telephone conference for [redacted] (6/24-26/08) and Schwarz-Pharma AG, Monheim, Germany (6/30/08 - 7/3/08). The investigations were conducted by a team of DSI scientists. The teleconference involved discussion of method validation and study sample analysis issues. This included request and review of additional data by DSI to address details of analytical conduct, and exchange of information, including follow-up and response to teleconference through electronic mails and documents. The evaluation of the significant issues and additional data provided during the teleconference follows: b(4)

[redacted] **(Study# SP645)** b(4)

5. Failure to document the activities of analysts when multiple analysts were involved in sample processing.

Two or more analysts were involved in processing samples (i.e. QC and subject samples) in a majority of the analytical runs. The extraction records for the runs do not identify the samples handled by each analyst and the specific extraction steps performed by each analyst. To assure accuracy of the concentration results, it is imperative that analysts processing subject samples also process QCs, and the subject samples and QCs processed by each analyst are identified. [redacted] informed DSI during the remote audit that they would revise their SOP to clearly document the activities of each analyst. b(4)

6. Lack of an electronic audit trail for integration of analyte peaks.

The data collection and integration software, Analyst Version 1.2, had an audit trail feature, but this feature was disabled during the study. Upon the request of DSI, [redacted] reintegrated the analytical runs using the default integration parameters b(4)

during the remote audit. Use of the default parameters did not change the acceptability of the analytical runs. Moreover, there were no significant changes between the reported subject samples concentrations and those that resulted from the reintegrated chromatograms.

7. Failure to determine the cause for the abnormal pharmacokinetic (PK) profile from a study subject.

The analytical report stated that Subject 80011 was re-dosed with oral formulation after the subject was found to exhibit abnormally low drug concentrations following the original oral dose. The firm reanalyzed the plasma samples for the subject collected following the iv dose, but did not reanalyze the plasma samples collected following the original oral dose and thus did not rule out analytical error. DSI is of the opinion that there is inadequate justification to discard the original oral data of this subject as there was no investigation to show that the abnormal concentrations from the original analysis were not due to an analytical error.

8. Failure to demonstrate working Lacosamide solution stability at 4-5 °C in water.

Working solutions were prepared in water and stored for up to 2 weeks at 4°C before preparing calibrator and QC solutions on each day of use. There was no data to support working solution stability in water at 4°C. ——— should provide this solution stability data. b(4)

Additional deficiencies that require corrective action but should not impact study outcomes include the following:

- Reports did not accurately identify all dates of sample receipt or describe the anticoagulant used.
- The firm lacked written criteria for reanalyzing study samples
- ——— relied on stability experiments conducted by other laboratories without assessing the validity of the data b(4)

Schwarz-Pharma AG, Monheim, Germany (Study # SP 658)

9. Documentation concerning usage of the working solutions is deficient. Specifically, there is no clear identification or cross reference to show which working solution was used

to prepare QCs and calibration standards employed in analytical and validation runs.

The integrity and accuracy of preparation of QCs and calibration standards generated in the study cannot be confirmed, as there was no source data to verify the lacosamide working solution used in the preparations.

10. **Late handwritten entries into Sample Preparation Forms had no cross references to other source documents and many of these entries were entered as late as several months.**

The accuracy of the information provided in the late entries cannot be confirmed. During the audit, Schwarz Pharma stated their analysts recorded the source data directly into the Sample Preparation Forms and there were no other reference source documents.

11. **Re-assays of many subject samples were not justified adequately. Specifically, according to the analytical study report, many samples were re-assayed for data confirmation due to deviation from the expected pharmacokinetic profile.**

Upon review of specific data provided electronically during the audit, DSI learned that many of these samples were re-assayed due to reasons such as suspicion of sample mix-ups, probable error during sample preparation, pipette or elution vial contamination, and low Internal Standard (IS) response. These reasons appear to be speculation and not based on documented evidence.

Several samples (attachment 1) were first identified for re-assay based on the deviation from the expected pharmacokinetic profile. From DSI viewpoint, these re-assays were conducted for pharmacokinetic reasons. The re-assay of these samples was not justified, as Schwarz Pharma did not establish objective criteria in an SOP for pharmacokinetic re-assays prior to analysis of study samples. The OCP reviewer should use the original data in the pharmacokinetic data analysis.

12. **Failure to confirm that samples in an analytical run were placed in the correct order prior to injection into the LC/MS/MS.**

This confirmation procedure along with proper documentation should be put in place to avoid the problem of sample mix-ups in future studies.

13. QC results that failed to meet the acceptance criteria were not included in the analytical run summary statistical calculations.

In order to provide an unbiased summary of analytical run performance, all QC results with no known source of errors (e.g., errors in sample preparation and/or processing, instrumental errors, etc.) should be included in the summary statistical calculations. Nevertheless, inclusion of all failed QC results by Schwarz-Pharma during the audit did not alter the adequacy of the precision and accuracy of the LC/MS/MS method.

Conclusions:

Following the above audits, the Division of Scientific Investigations concludes that:

a. The authenticity of the test and reference products used in Studies# SP 645 and SP 658 cannot be assured as the clinical site failed to randomly select and retain the reserve drug samples. Therefore, Study No. 658 and No. 645 fails to meet the regulatory requirements for the retention of reserve samples for bioequivalence studies [21 CFR 320.38 and 63]. Also, the lot of test drug used in Study No. 645 cannot be assured.

Study# SP 645

b. There was no data to support working solution stability for lacosamide in water at 4°C (Item 8). To assure accuracy of the lacosamide pharmacokinetic data generated in the study, b(4)
—— should provide a minimum of two weeks solution stability data in water at 4°C.
c. There is no justifiable reason to discard the original pharmacokinetic data following oral dose for Subject 80011 (Item 7).

Study# SP 658

d. Due to deficiencies in documentation, the integrity and accurate preparation of QCs and calibration standards generated in the study cannot be confirmed (Items 9 and 10).

e. The re-assay of subject samples for data confirmation (Item 11) was not justified. Schwarz Pharma did not establish objective criteria for pharmacokinetic re-assays prior to analysis of study samples. The OCP reviewer should use the original data in the pharmacokinetic data analysis.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Hyojong Kwon, Ph.D.

Michael F. Skelly, Ph.D.

Xikui Chen, Ph.D.

Martin K. Yau, Ph.D.

Final Classifications:

VAI - [redacted]
VAI - [redacted]
VAI - [redacted]
VAI - Schwarz-Pharma AG, Monheim, Germany

b(4)

cc:
DSI/Vaccari
DSI/GLPBB/Kwon/Skelly/Chen/Yau/CF
OTS/OCP/DCP1/Tandon/Uppoor
OND/ODEI/DNP/Ware/NDA 22-254

HFR-CE3565/Mangalindan
HFR-PA1530/Shrifter
Draft: HK 7/7/08; XC 6/19/08; MFS 7/2/08; MKY 7/16/08
Edit: MFS 7/18/08; MKY 7/22/08; SS 7/23/08; JO 7/23/08
DSI: BE-5830; O:\bioequiv\EIRCover\22254sch.vim.doc
FACTS: 916149

Attachment 1

Reassays

Subject	1. Assay	2. Assay	Concentration reported	Reason
80002 P3 4h				Fault during sample preparation, fault during addition of ISTD
80009 P2 60h				Probably fault during sample preparation, 60h sample mixed up with 72h sample
80009 P2 72h				Probably fault during sample preparation, 72h sample mixed up with 60h sample
80010 P2 48h				Probably fault during sample preparation, 48h sample mixed up with 60h sample
80010 P2 60h				Probably fault during sample preparation, 60h sample mixed up with 48h sample
80015 P1 3h				- (part of the sequence, but reported)
80015 P1 4h				Suspect of mix-up during sample preparation, not confirmed, probably error during sample preparation
80015 P1 6h				Suspect of mix-up during sample preparation, not confirmed, probably error during sample preparation
80015 P1 8h				Suspect of mix-up during sample preparation, not confirmed, probably error during sample preparation
80015 P1 12h				- (part of the sequence, but reported)
80016 P2 4h				Fault during sample preparation, sample mixed up with 48h sample, sample processed with 250µL instead of 48h sample
80016 P2 6h				Fault during sample preparation, sample mixed up with 60h sample, sample processed with 250µL instead of 60h sample
80016 P2 8h				- (part of the sequence)
80016 P2 12h				- (part of the sequence)
80016 P2 24h				- (part of the sequence)
80016 P2 36h				- (part of the sequence)

b(4)

Reassays

Subject	1. Assay	2. Assay	Concentration reported	Reason
80016 P2 48h				Fault during sample preparation, sample mixed up with 4h sample, sample processed with 500 µL instead of 4h sample
80016 P2 60h				Fault during sample preparation, sample mixed up with 6h sample, sample processed with 500µL instead of 6h sample, no plasma available for reassay
80016 P3 4h				Fault during sample preparation, sample mixed up with 48h sample, sample processed with 250µL instead of 48h sample
80016 P3 6h				- (part of the sequence)
80016 P3 8h				Fault during sample preparation, sample mixed up with 72h sample, sample processed with 250 µL instead of 72h sample
80016 P3 12h				- (part of the sequence)
80016 P3 24h				- (part of the sequence)
80016 P3 36h				- (part of the sequence)
80016 P3 48h				Fault during sample preparation, sample mixed up with 4h sample, sample processed with 500 µL instead of 4h sample
80016 P3 60h				- (part of the sequence)
80016 P3 72h				Fault during sample preparation, sample mixed up with 8h sample, sample processed with 500 µL instead of 8h sample
80023 P2 0h				Probably fault during sample preparation, elution vial or pipet tip contaminated
80023 P3 0h				erroneously reassayed
80023 P3 0.25h				Probably fault during sample preparation, peak area of ISTD lower
80023 P3 0.5h				Probably fault during sample preparation, peak area of ISTD lower

b(4)

Reassays

Subject	1. Assay	2. Assay	Concentration reported	Reason
80024 P1 60h				Fault during sample preparation, 60h mixed up with 72h during sample preparation
80024 P1 72h				Fault during sample preparation, 72h mixed up with 60h during sample preparation

b(4)

APPEARS THIS WAY
ON ORIGINAL

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/s/

Hyojong Kwon
7/25/2008 03:17:01 PM
BIOPHARMACEUTICS
Dr.Viswanathan signed the paper copy on 7/25/08.

Executive CAC
Date of Meeting: July 8, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Anne Pilaro, Ph.D., DBOP, Alternate Member
Lois Freed, Ph.D., DNP, Supervisor
Ed Fisher, Ph.D., DNP, Presenting Reviewer

Author of Draft:

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 22-253, 22-254
Drug Name: Lacosamide (SPM927) Tablet, Injection
Sponsor: Schwarz Biosciences

Mouse Carcinogenicity Study:

Key study findings: Clinical signs demonstrated that higher doses would not have been tolerated. No significant clinical signs were noted at 20 mg/kg/d of SPM 927. At 60 mg/kg/d, ataxia and reduced activity were reported for the first 8 weeks on study but abated until Week 35 when decreased activity was noted in males and Week 54 when it was noted in females. Neither tremors nor convulsions were reported for this dose group. In the animals treated with 180 mg/kg/d, ataxia, decreased activity and "abdominal position" were observed for almost all of the animals throughout the study. Tremors were reported during the first 11 weeks on study as well as clonic convulsions in all treated animals at this dose. These tremors/convulsions started 5-20 minutes after dosing and lasted for up to 3 hrs. While the males in this group showed a -10% difference in body weight when compared to controls, it appears that the severe clinical signs did not appreciably affect the physiology of the affected animals. No additional adverse effects were recorded for any of the animals on study to include hematology, clinical chemistries, organ weights, gross or histologic pathology.

Adequacy of the carcinogenicity study and appropriateness of the test model: The CD-1 mouse is considered an appropriate model for evaluation of carcinogenic potential. The high dose (180 mg/kg/d) in this study elicited significant clinical signs of toxicity (tremors, clonic convulsions, ataxia, hypoactivity) so this dose is considered the maximum tolerated dose. No increase in mortality was found at any dose tested.

Evaluation of tumor findings: There were no increases in tumor incidence or type in any dose group.

Rat Carcinogenicity Study:

Key study findings: Clinical signs demonstrated that higher doses would not have been tolerated. No significant clinical signs were seen at 40 or 80 mg/kg/d of SPM 927. At the high dose (Males: 160 mg/kg/d; females: 160/180/200 mg/kg/d), clonic convulsions with/without "abdominal position" were reported in Weeks 4-18 in about 1/3- 1/2 of the animals; hypoactivity was noted from Weeks 19-29 in this dose group. Once the dose in females was increased to 180 mg/kg/d, an increase in "abdominal position" was recorded for a couple of days in approximately1/2 of the animals. Similarly, when the dose was again increased to 200 mg/kg/d, increased "abdominal position" and hypoactivity were reported for most of the females and persisted for approximately 2 weeks. These signs were elicited 5-20 minutes post-dosing and persisted for up to 2 hrs. At 60

mg/kg/d, ataxia and reduced activity were reported for the first 8 weeks on study but abated until Week 35 when decreased activity was noted in males and Week 54 when it was noted in females. Neither tremors nor convulsions were reported for this dose group. In the animals treated with 180 mg/kg/d, ataxia, decreased activity and "abdominal position" were observed for almost all of the animals throughout the study. Tremors were reported during the first 11 weeks on study as well as clonic convulsions in all treated animals at this dose. These tremors/convulsions started 5-20 minutes after dosing and lasted for up to 3 hrs. While the males in this group showed an -8% difference in body weight when compared to controls at the end of the study, it appears that the severe clinical signs did not appreciably affect the physiology of the affected animals. No additional adverse effects were recorded for any of the animals on study to include hematology, clinical chemistries, organ weights, gross or histologic pathology. No neoplastic lesions were found related to treatment with SPM 927.

Adequacy of the carcinogenicity study and appropriateness of the test model: CD rats are an acceptable model to determine the carcinogenic potential of pharmaceuticals. At the high dose, significant clinical signs of toxicity were reported (clonic convulsions, "abdominal position" and hypoactivity) so the top dose is considered a maximal tolerated dose even though no increase in mortality was observed.

Evaluation of tumor findings: There were no increases in tumor incidence or type in any dose group.

Executive CAC Recommendations and Conclusions:

Mouse study:

- The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the doses used.
- The Committee agreed that the study was negative for any statistically significant drug-related neoplasms.

Rat study:

- The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the doses used.
- The Committee agreed that the study was negative for any statistically significant drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DNP
/LFreed, DNP
/EFisher, DNP
/JWare, DNP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
7/10/2008 11:50:16 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 29, 2008

TO: Matt Sullivan, Regulatory Project Manager
Jackie Ware, Regulatory Project Manager
Dr. Mwango Kashoki, Medical Officer
Dr. Norman Hershkowitz, Medical Officer

FROM: Sheryl Gunther, Pharm.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: [redacted], 22-253, 22-254 [redacted] b(4)

APPLICANT: Schwarz Biosciences, Inc.

DRUG: Harkoseride/Vimpat® (lacosamide)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: (1) adjunctive treatment of partial onset seizures in patients with epilepsy
(2) management of [redacted] pain associated with diabetic peripheral neuropathy b(4)

CONSULTATION REQUEST DATES: December 3, 2007 and January 2, 2008

DIVISION ACTION GOAL DATE: July 28, 2008

PDUFA DATE: July 28, 2008

I. BACKGROUND:

Lacosamide is a new molecular entity developed by Schwarz Biosciences, Inc. for two indications: (1) adjunctive treatment of partial onset seizures in patients with epilepsy and (2) management of [redacted] pain associated with diabetic peripheral neuropathy. Three dosage forms have been developed, including immediate release tablets, an injection, [redacted] b(4)
[redacted] The subject of NDAs 22-253 (epilepsy [redacted] is immediate release tablets, while NDAs 22-254 [redacted] provide for the use of lacosamide injection [redacted] for the treatment of epilepsy. For the epilepsy indication, Drs. Michael Sperling's (SP754), Gregory Krauss' (SP754), Zdravka Poljakovic's (SP755), and Sanja Hajnsek's (SP755) sites were selected for inspection due to enrollment of large numbers of study subjects. For the neuropathic pain indication, [redacted]
[redacted]). The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare.

The protocols inspected include:

[redacted] b(4)

- **Protocol**: # SP754, entitled "A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (400 and 600mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization"
- **Protocol**: #SP755, entitled "A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization"

[redacted] b(4)

b(4)

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Protocol #	Inspection Date	Final Classification
Dr. Michael Sperling, Site #060 Thomas Jefferson University Hospital Jefferson Comprehensive Epilepsy Center 900 Walnut Street, Suite 200 Philadelphia, PA 19107	Protocol #SP754	April 21-24, 2008	Pending (NAI)
Dr. Gregory Krauss, Site #007 Johns Hopkins Hospital 600 N. Wolfe Street Meyer 2-147 Baltimore, MD 21287-7247	Protocol #SP754	February 18-21, 2008	NAI
Dr. Zdravka Poljakovic, Site #021 University Hospital Center Zagreb Department of Neurology Ctr. For Epilepsy Kispaticeva 12 10000 Zagreb Croatia	Protocol #SP755	March 10-14, 2008	Pending (VAI)
Dr. Sanja Hajnsek, Site #023 University Hospital Center Zagreb Department of Neurology Ctr. For Epilepsy Kispaticeva 12 10000 Zagreb Croatia	Protocol #SP755	March 17-21, 2008	Pending (VAI)
Schwarz Biosciences, Inc. 8010 Arco Corporate Drive, Suite 100 Raleigh, NC 27617	Protocol — SP754, SP755, —	May 19-23, 2008	Pending (NAI)

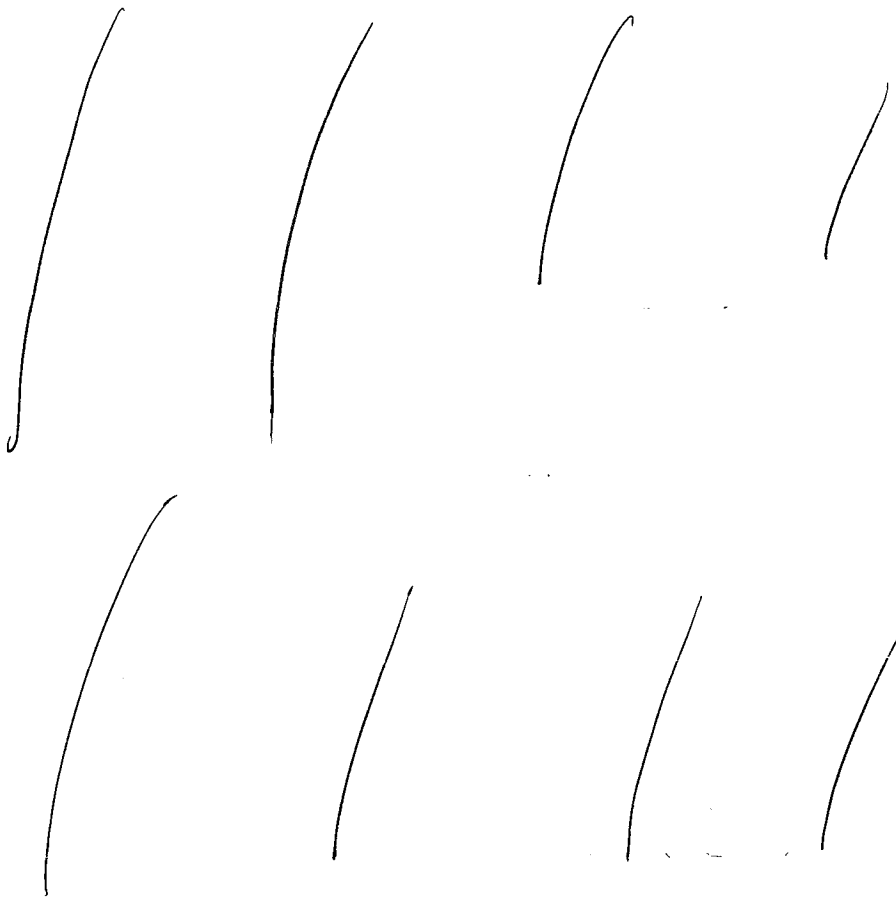
b(4)

b(4)

b(4)

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

b(4)



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3. Dr. Michael Sperling, Site #060
Thomas Jefferson University Hospital
Jefferson Comprehensive Epilepsy Center
900 Walnut Street, Suite 200
Philadelphia, PA 19107

   a. **What was inspected:** For protocol SP754, 22 subjects were screened, 18 subjects were randomized, and 16 subjects completed the study. Informed consent documents for all subjects were reviewed. An audit of 18 subjects' records was conducted.

   b. **General observations/commentary:** No significant regulatory violations were noted.

Observations noted above are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

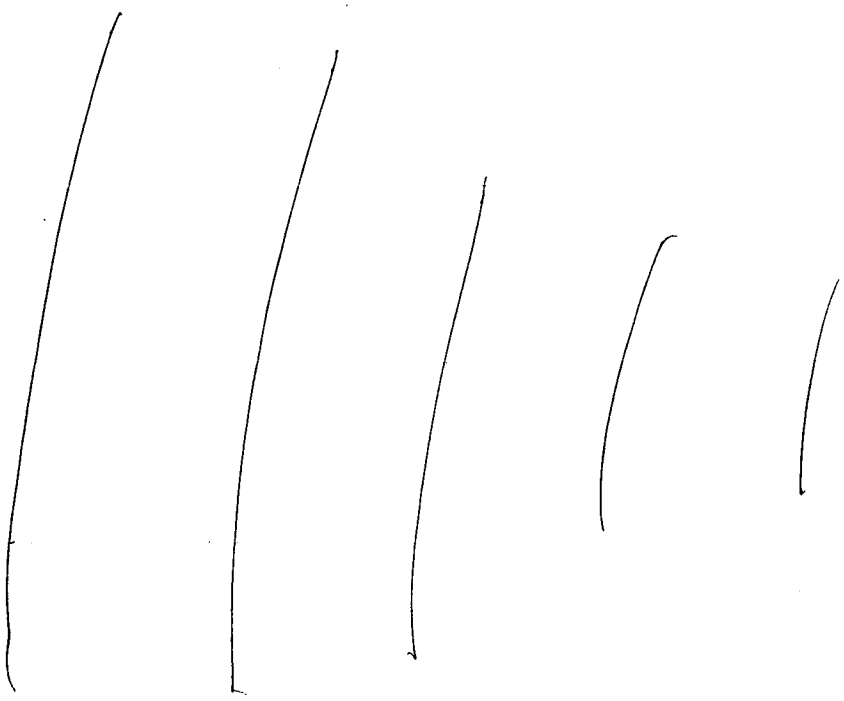
c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

4. Dr. Gregory Krauss, Site #007
Johns Hopkins Hospital
600 N. Wolfe Street
Meyer 2-147
Baltimore, MD 21287-7247

a. **What was inspected:** For protocol SP754, 17 subjects were screened, 15 subjects were randomized, and 15 subjects completed the study. An audit of all subjects' records was conducted, including informed consent documents.

b. **General observations/commentary**: No significant regulatory violations were noted.

c. **Assessment of data integrity**: Data for this site appear acceptable in support of the pending application.



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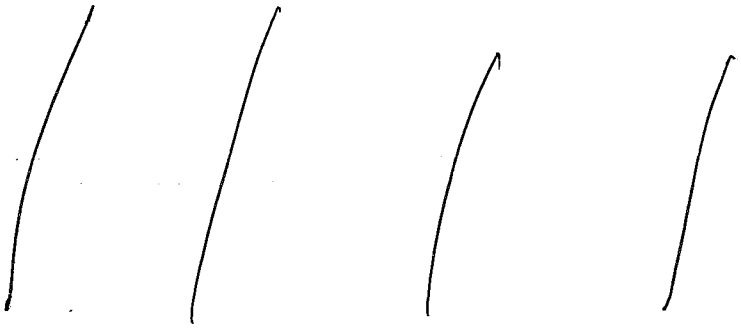


b(4)

6. Dr. Zdravka Poljakovic, Site #021
University Hospital Center Zagreb
Department of Neurology
Ctr. For Epilepsy
Kispaticeva 12
10000 Zagreb
Croatia

a. **What was inspected**: For protocol SP755, 20 subjects were screened and randomized, and 16 subjects completed the study. Informed consent documents for all subjects were reviewed. An audit of 18 subjects' records was conducted.

b. **General observations/commentary**:

The inspection revealed protocol violations with respect to a dosage reduction following an adverse event (mild blurred vision) experienced by Subject 102115 between study visits 4 and 5. Specifically, the subject returned for a clinic visit 7 days following the dose reduction and 10 days following the onset of the adverse event, outside of the 2-day period specified in the protocol. Additionally, the protocol specified that subjects who required a dose reduction at visit 4 were to be tapered off the trial medication and withdrawn from the trial. Subject 102115 was not withdrawn from the trial, and allowed to continue at the previous full dosage and later entered into an extended open label study (SP774).

Additionally, discrepancies were found between the source data documents and case report forms. Specifically, for three of 16 subjects, information noted in the case report forms was not always present in the source documents. For Subjects 102108, 102109, and 102111, the case report forms indicated that a urine sample was collected, whereas source documents did not reflect that a urinalysis was performed. For Subject 102111, the case report form noted that a urine pregnancy test was performed, but this information was not present in the source documents.

 b(4)

Observations noted above are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

c. **Assessment of data integrity:** The review division should evaluate the significance and impact, if any, of Subject 102115's participation in the study following an adverse event requiring a dosage reduction as described above. Otherwise, data from this site appear acceptable for use in support of this NDA.

7. Sanja Hajnsek, Site #021
University Hospital Center Zagreb
Department of Neurology
Ctr. For Epilepsy
Kispaticeva 12
10000 Zagreb
Croatia

a. **What was inspected**: For protocol SP755, 18 subjects were screened and enrolled, and 12 subjects completed the study. Informed consent documents for all subjects were reviewed. An audit of 18 subjects' records was conducted.

b. **General observations/commentary**:

The inspection revealed minor instances of original data in source records obscured by white out and ink.

Observations noted above are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

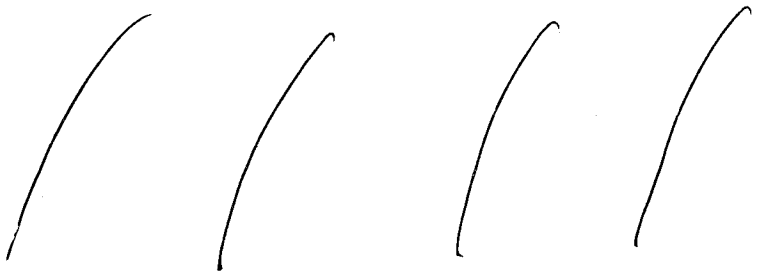
8. Schwarz Biosciences, Inc.
8010 Arco Corporate Drive, Suite 100
Raleigh, NC 27617

a. **What was inspected:** The inspection audited protocol —), b(4)
— , SP754 (sites 060 and 007), SP755 (sites 021 and 023), and
— The inspection included review of standard operating procedures and monitoring reports, as well as the investigation of —

b(4)

 b(4)

b. **General observations/commentary**: No significant regulatory violations were noted.



b(4)

Observations noted above are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

c. **Assessment of data integrity**: Data for this sponsor appear acceptable in support of the pending application.

b(4)

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As mentioned above, [redacted]

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The inspection of the other sites found no significant regulatory violations. Data generated from the remaining clinical sites, and monitored by the sponsor, reportedly capture primary efficacy endpoints as specified in the protocol, and appear acceptable for use in support of the pending application.

Observations noted above are based on communications from the field investigators and FDA Form 483s when available. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Sheryl Gunther, Pharm.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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/s/

Sheryl Gunther
6/11/2008 12:50:53 PM
PHARMACOLOGIST

Constance Lewin
6/11/2008 04:03:14 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: CDER OSE Consults

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Jackie Ware, Division of Neurology Products
301-796-1160

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/27/08 - request sent via email on 4/17/08		22-253 22-254 b(4)	Updated Carton & Container Labeling	April 16, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lacosamide Tabs, Injection, b(4)	High	anti-conconvulsant	5/27/08

NAME OF FIRM: Schwarz BioSciences

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

On April 9, 2008, Schwarz submitted updated carton & container labels to NDA 22-253; the electronic link is \\CDSESUB1\EVSPROD\NDA022253\0008. This link was emailed to OSE on 4/17/08. Because these labels are very different from the original labels and → lacosomide products need to be reviewed, it was agreed on 4/17/08 b(4) that a new consult would be sent. In the interest of facilitating the review process, OSE provided a new RCM# prior to DNP sending the formal consult request.

As such, **the OSE RCM# for this consult request is RCM# 2008-633.**

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Jackie Ware	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Jackie Ware
5/27/2008 04:04:05 PM
Request & documents emailed to OSE on 4/17/08; RCM # already assigned - RCM# 2008-633.

Ware, Jacqueline H

From: DOttavio Misty [Misty.DOttavio@ucb-group.com]
Sent: Friday, May 23, 2008 1:28 PM
Ware, Jacqueline H
Cc: Blumberg Alan
Subject: List of Requests
Attachments: FDA Requests 23May08.pdf; Outstanding Requests 23May08.pdf; emfinfo.txt

Hi Jackie,

Please find attached an updated list of all the requests received and the list of outstanding requests.

Let me know if you have any questions.

Have a great weekend,

Misty

(A)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
12/10/2007						
	22-253					
		Division of Neurology Products				
		Response Complete ☑	From 74-day letter: 2. The PK-PD modeling report for epilepsy is not under the folder 5.3.4 (reports for human PD studies). It is also not present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies). Please verify that all studies/Modeling reports submitted to the NDA are listed under the Tabular listing of studies.	Lifecycle	1/23/2008	Submission Sequence 0003
		Response Complete ☑	From 74-day Letter: 1. The bioanalytical report for Study SP645 could not be located within the study report. The bioanalytical tests were performed at [redacted] but the report is not included. Please submit this information soon (e.g., within 2 weeks)	Lifecycle b(4)	1/23/2008	Submission Sequence 0003
		Response Complete ☑	From 74-day Letter: 1.Please clarify whether the MedDRA version used in this application is Version 9.1.	Email Lifecycle	12/19/2008 1/23/2008	It was confirmed that the MedDRA version used in this application is Version 9.1. No formal response required. Submission Sequence 0003
		Response Complete ☑	From 74-day Letter: 5.For lacosamide injection (NDA 22-254), with respect to product labeling, [redacted]	Email b(4)	12/19/2007	[redacted] b(4)
		Response Complete ☑	From 74-day Letter: 3.The formulation of the 50 mg lacosamide clinical tablets is not provided in the original NDA (22-253). Provide the quantitative unit composition for all strengths of each formulation that was used in clinical studies to support this application.	Email Lifecycle	12/19/2007 1/23/2008	Status of response provided Submission Sequence 0003

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete ☑	From 74-day Letter: 4. For lacosamide tablets, the container closure documetation for PVC/PVDC-Aluminum blisters and HDPE bottles is provided in the application. Clarify whether the blisters will be used for commercial distribution or professional samples and provide the appropriate container labels for review.	Lifecycle Lifecycle	1/23/2008 3/20/2008	A partial response was included in Submission Sequence 0003 to confirm that the blisters will be used for professional samples. The draft labels will be provided to the Division as soon as available. Submission Sequence 0006
		Response Complete ☑	From 74-day Letter: 7.Please provide a joint Adverse Event dataset for placebo-controlled studies in both epilepsy and diabetic neuropathic pain.	Mail Lifecycle	1/8/2008 1/23/2008	Requested datasets were provided by DVD. Submission Sequence 0003
		Response Complete ☑	From 74-day letter: 6.a. Please provide tables of serious adverse events in placebo-controlled studies for both epilepsy and diabetic neuropthic pain together, by MedDRA SOC and by dose. The table should be similar to the table below, but include data for both S1 pools (epilepsy and diabetic neuropathic pain) considered together. b. Please also provide summary tables of discontinuations due to adverse events in placebo-controlled studies for both epilepsy and diabetic neuropthic pain together, by MedDRA SOC and dose.	Email Lifecycle	12/19/2007 1/23/2008	Status of response provided Submission Sequence 0003

1/7/2008

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Division of Neurology Products

		Response Complete ☑	Please provide a single adverse events dataset and a single disposition dataset for all placebo-controlled studies with lacosamide (excluding the open-label phase, for both indications).	Mail Lifecycle	1/8/2008 1/23/2008	Requested datasets provided by DVD. Submission Sequence 0003

1/14/2008

22-253

Division of Neurology Products

Request Date	*NDA#*	*Division*	*Request*	*Reponse Type*	*Reponse Date*	*Response*
		Response Complete ☑	1. Your description of the safety pools in page 17 of the Clinical Summary indicates that the EP S2 pool includes studies SP607 and SP615. However, the ISS dataset does not include patients from studies 607 and 615. Please clarify why. Also provide Lacosamide tablets exposure in patient years as presented in page 22 of the Clinical Summary, without these two studies.	Email Email	1/15/2008 1/15/2008	Clarification requested FDA responded and requested that we disregard request #1.
		Response Complete ☑	2. You state that 1327 unique patients were exposed to the oral tablet formulation in the phase 2/3 epilepsy studies. It is unclear how many of these rolled over into extension/open label studies from the active and placebo groups in placebo-controlled studies, and how many were new patients. Please clarify.	Email Lifecycle	2/8/2008 2/13/2008	 Submission Sequence 0004
		Response Complete ☑	3. Please provide line listings of patients with adverse events that led to dose reduction in the EP trials, including the dose at which the event occurred, the outcome (resolved or eventually led to discontinuation) and the final dose at the end of the study or time of withdrawal in the S1 and S2 pools.	Lifecycle	2/13/2008	Submission Sequence 0004
		Response Complete ☑	4. Provide a summary table of adverse events that led to dose reduction and/or discontinuation by SOC and PT term (similar to tables EP 6.29.1 and EP 6.30.1 of the Clinical Summary of Safety, respectively, but with dose reduction + discontinuation instead of only discontinuations). If these analyses have already been submitted, please direct the reviewer to the exact location.	Lifecycle	2/13/2008	Submission Sequence 0004
		Response Complete ☑	5. Please clarify how many patients discontinued because of consent withdrawal and had had an adverse event that required dose reduction.	Email Lifecycle	2/8/2008 2/13/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0004
		Response Complete ☑	6. We acknowledge that the disposition and AE datasets submitted with the original application include maximum treatment dose columns, but they provide a dose range, not the actual maximum dose received by each patient. Please provide the maximum dose taken at any time during the double blind and the OL periods for each patient in EP Pool 1 and 2.	Email Lifecycle	2/8/2008 2/13/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0004
		Response Complete ☑	7. Patient 756/754012317 was found dead at home. Please provide some supportive evidence to your assumption that this was a case of SUDEP. Otherwise, it could have been plain sudden death.	Lifecycle	2/13/2008	Submission Sequence 0004

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete ☑	8. There are discrepancies between some of the ages listed in the summary table of deaths in pg. 120 of the Summary of Clinical Safety, and the ages stated in the narratives. Similarly, there are discrepancies between the days on treatment at the time of death listed in the summary table and those mentioned in the narratives. Please clarify and revise accordingly.	Lifecycle	2/13/2008	Submission Sequence 0004
		Response Complete ☑	9. As per the summary table of deaths, patient 667/667012803 died on relative day 21 of LCM treatment. However, the narrative states that it is unclear whether the patient was taking medication or not during the last 3 weeks in the trial. A calculation of days on treatment based on the starting date in the disposition dataset suggests that the duration of treatment was either 68 days or 127 days. Please clarify where the day #21 came from.	Email Lifecycle	2/8/2008 2/13/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0004

1/29/2008

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Division of Neurology Products

		Response Complete ☑	Regarding item #4 of our January 14, 2008 request (included below for reference), please also submit a summary table of AE that led to dose reduction and/or discontinuation by SOC and PT in Pool EP S1 by dose at onset.	Lifecycle	2/13/2008	Submission Sequence 0004

1/31/2008

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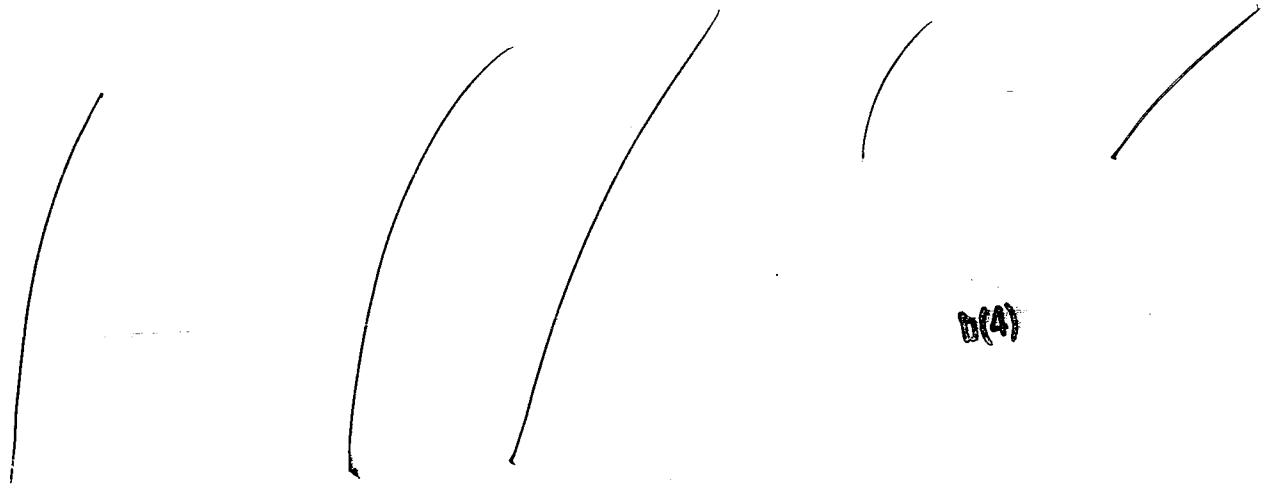
Division of Neurology Products

		Response Complete ☑	1. The epilepsy placebo-controlled safety pool (EP Pool S1) includes 364 patients randomized to placebo. Tables EP 6.47.1 (Incidence of common treatment emergent adverse events [TEAEs] resulting in discontinuation in EP pool S1 by dose at onset) and EP 6.49.1 of the ISS (Incidence of TAEs during the treatment phase by dose at onset in population Pool S1), show 781 patients receiving placebo. Please clarify.	Email Lifecycle	2/8/2008 2/13/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0004

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete ☑	2. The number of AEs in the "LCM total" group in table 6.47.1 of the ISS (Incidence of common TEAEs resulting in early discontinuation from the treatment phase in population Pool S1 by dose at onset) do not match some of the numbers in EP.6.29.1 of the ISS (Incidence of TEAEs resulting in early discontinuation from the treatment phase in population Pool S1 by randomized dose). For instance, in table 6.29.1, there are 9 patients who underwent drug discontinuation in the "Investigations" SOC in the "LCM total" column. However, table 6.47.1 only lists two discontinuations due to Investigations in this population, one at the 100 mg/d dose and one at the 200 mg/day dose. Please clarify this discrepancy.	Email Lifecycle	2/8/2008 2/13/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0004
		Response Complete ☑	3. Please submit a summary table of Serious TAEs during treatment phase by dose at onset in EP Pools S1 and S2 or direct the reviewer to the exact location in the submission where this information is located.	Lifecycle	2/13/2008	Submission Sequence 0004
		Response Complete ☑	4. Please clarify whether AEs that occurred within 30 days after the last dose of study medication were included in the analyses of the epilepsy studies. If so, in which pool and study phase?	Lifecycle	2/13/2008	Submission Sequence 0004



Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
[redacted]						
2/7/2008	22-253	Division of Neurology Products	Response Complete ☑ For Study SP657, the within study bioanalytical report has been provided for assessing lacosamide and its metabolite in human saliva. The within study bioanalytical report for assessing the drug in human plasma could not be located. Please provide this. If already submitted, please indicate its location.	Email	2/7/2008	Location for request provided by email.

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Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
2/14/2008						
	22-253					
		Division of Neurology Products				
		Response Complete ☑	We have reviewed your comment and response to FDA 1/14/08 Question 6 (included below for ease of reference) and have the following clarification. Comment/Response from Schwarz: "In reference to FDA 1/14/08 Question 6: We acknowledge that the disposition and AE datasets submitted with the original application include maximum treatment dose columns, but they provide a dose range, not the actual maximum dose received by each patient. Please provide the maximum dose taken at any time during the double blind and the OL periods for each patient in EP Pool 1 and 2. Sponsor's Response: The Integrated EXPOSURE analysis file has the variable MAXOVER which is the maximum LCM dose taken at any time during exposure to LCM for the combined double-blind and OL periods for each subject in EP Pool S2. This is a 1 record per subject file for epilepsy and can be easily merged with the Disposition and/or AE files." FDA clarification: This response does not fully address our request. Please provide the listing of subjects who received LCM doses higher than the randomization dose in the EP Pool S1 and subjects who received LCM doses above 800 mg/day in EP S2. With regard to your February 11, 2008 email, which requests feedback about our January 14, 2008 Question 4, we agree that the analysis by dose at onset in S2 is difficult to interpret. Therefore, we ask that you respond to the following request instead of the original request described in FDA 1/14/08 Question 4. Please provide the analysis of TAES that resulted in early discontinuation or dose reduction by dose at onset and by randomization dose in Pool EP S1.	Email Lifecycle	2/22/2008 2/25/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0005

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1 Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
2/26/2008						
	22-253					
		Division of Neurology Product				
	Response Complete ☑		Please explain why the lacosamide Tmax values were greater than the infusion duration (1 - 3 hours) in about 25% of the subjects in the 15, 30 and 60 minutes infusion groups in studies SP645 and SP658	Email	3/5/2008	Response sent by email, formal response to be submitted in the next lifecycle.
				Lifecycle	3/20/2008	Submission Sequence 0006
3/3/2008						
	22-253					
		Division of Neurology Products				
	Response Complete ☑		1. Your Feb 19, 2008 response lists 11 patients from EP Pool S2 who received LCM doses >800 mg daily. It is our impression that the maximum dose recommended in the open label studies was 800 mg daily. Please clarify: a. Whether dosing >800 mg daily was accidental or intentional, b. Whether dosing >800 mg daily was associated with adverse events in these patients, c. Whether any case suggests potential for drug abuse. 2. Table EP. 7.15.1 (Incidence of treatment emergent marked abnormalities during the treatment phase –chemistry) in Pool S1 submitted with the original NDA seems to be missing the analysis of Triglycerides. Please provide such analysis. 3. As per AE dataset, Subject 754011401 patient developed QTC prolongation on day 1, on LCM 100 mg/day. The reviewer has not been able to find the narrative and CRF for this patient. Please submit or direct the reviewer to the exact location of this information.	Email	3/5/2008	Concerning request No. 3. below, here is the path to where the narrative is located: The narrative for Subject 754011401 is located within Section 15.3.4 of the ISS (Narratives for other significant AEs). There is an overall table within Section 15.3.4 which identifies all trials for which there are narratives for other significant AEs. If you "select" SP754 from this table, it will hyperlink to the SP754-specific table for other significant AEs. Within this table, there is a line for Subject 754011401. If you "select" this subject, it will hyperlink to the narrative for this subject.
				Lifecycle	3/20/2008	Submission Sequence 0006

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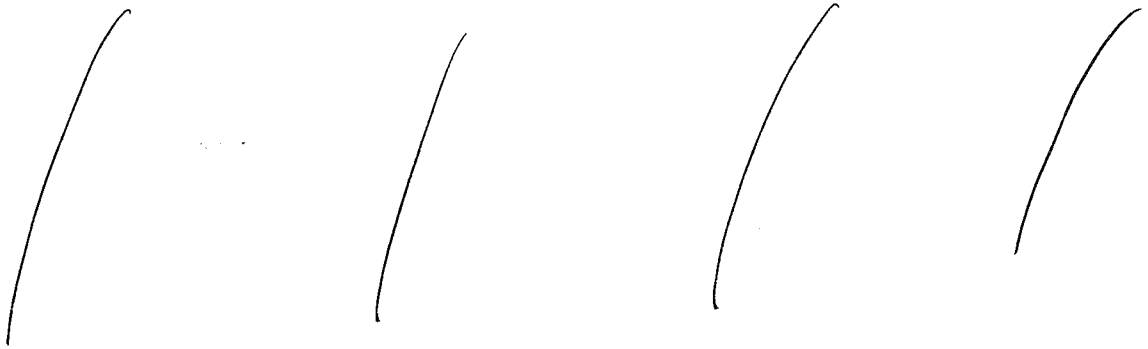
Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response



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3/7/2008

22-253

Division of Neurology Products

Response Complete ☑	1. Subject ID# 75411401 discontinued from the trial because of QTc prolongation. However, the reason for discontinuation for this patient was "Protocol violation" because the prolongation was present at baseline and the patient had been randomized by error. As per the amended CRF, three ECGs were done prior to administration of trial medication, at 14:16, 14:31 and 14:49 on May 19, 2004. However, the first LCM dose is recorded as given at 11.:30. Please clarify why the timing of the ECGa was amended on June 18, 2004, whether the baseline ECGs were done before or after the first LCM dose and whether the patient continued taking LCM until May 24, 2004. 2. Additionally, a footnote to the table in pg 103 of the Cardiac report indicates that non-compliance for ECG measurements was found in site 012. Please clarify what kind of non-compliance was found at that site.	Lifecycle Email	3/20/2008 3/26/2008	Question 2 included in Submission Sequence 0006 Question 1 was emailed and will be submitted in the next lifecycle submission.
Response Complete ☑	Please provide the ecg.xpt file from the ISS for EP Pool S1 only on disc.	Mail	3/11/2008	Requested dataset sent by DVD

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response

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3/11/2008

22-253

Division of Neurology Products

Response Complete ☑	1. Based on our request from March 3, please provide two analyses: one for TG >= 1.5 X ULN and other for TG >= 2 X ULN	Lifecycle	3/20/2008	Submission Sequence 0006	
Response Complete ☑	2. Please provide analyses of transaminase levels >= 2 X ULN in EP pool S1	Email	3/13/2008	Response provided and will be incorporated in next life cycle submission.	
		Lifecycle	3/20/2008	Submission Sequence 0006	
Response Complete ☑	3. Your mentions 7 subjects who dropped out of the migraine study because of potentially cardiovascular-related adverse events during the last year. Please provide additional information from the cases who dropped from the migraine study because of MI, syncope, chest pain, high blood pressure and palpitations.	Lifecycle	4/14/2008	Submission Sequence 0009	

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Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response

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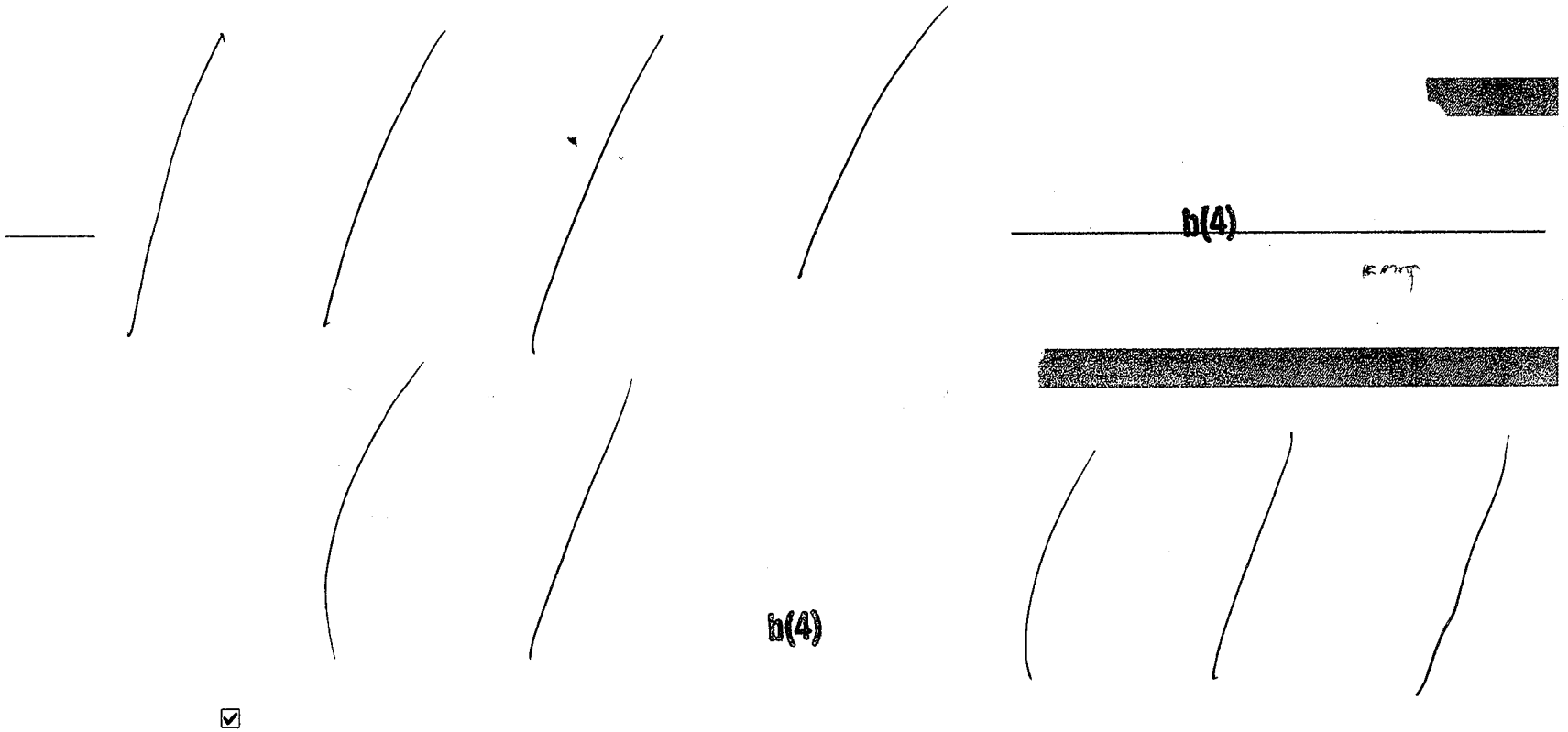
b(4)

3/20/2008

22-253

Division of Neurology Products

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete	CMC Letter dated 03/20/08	Lifecycle	4/18/2008	Submission Sequence 0010 Partial responses submitted.
		☑		Lifecycle	4/30/2008	Submission Sequence 0011 All outstanding responses submitted.



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4/2/2008

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
22-253						
		Division of Neurology Products				
		Response Complete ☑	1. In study 667 protocol amendment 3, it was stated that the number of subjects to be enrolled was re-estimated and that the number needed for the primary analysis remained unchanged. Please indicate the date that this re-estimation was done as well as whether it involved any unblinding of the internal study data. Please provide any relevant documentation. 2. The protocols of study 754 and study 755 were also amended after the studies were underway to increase the sample size for the primary analysis. A) Were there any unblinded interim looks at the data? Please provide any relevant documentation. B) Was any unblinded sample size re-estimation done using internal trial data? C) Who had access to the data during the trials and were there any limits on their access?	Email Lifecycle	4/11/2008 4/18/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0010

4/4/2008

22-253						
		Division of Neurology Products				

APPEARS THIS WAY
ON ORIGINAL

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete ☑	Drug Substance: For drug substance impurity [redacted] you have proposed a specification limit of NMT [redacted] which is above the ICH qualification limit of 0.15%. This impurity was adequately tested in the chronic oral toxicology (6-month rat, 12-month dog), reproductive toxicology, and genetic toxicology studies for lacosamide. However, [redacted] was not detectable in the drug batch used in the rodent carcinogenicity studies. Carcinogenicity testing of impurities is not generally required. However, there is concern regarding the genotoxic potential of [redacted] because of the positive results obtained in the in vitro mouse lymphoma tk assays, both in the absence and presence of metabolic activation. Therefore, you will need to either lower the drug substance specification to a level that would result in a daily dose of [redacted] mg/day or conduct genetic toxicity testing (in vitro Ames and in vitro mouse lymphoma tk assays) of [redacted] directly in order to support the proposed specification limit. IV formulation drug product: For drug product degradant [redacted] you have proposed a specification limit of NMT [redacted] %, which is above the ICH qualification limit of 0.20%. While the [redacted] provides an acceptable means of qualification, you [redacted] did not include an [redacted] which we require for establishing the safety of an impurity for drugs of this category (chronic use, antiepileptic). Without information on the potential developmental toxicity of [redacted] we cannot approve an acceptance criterion greater than 0.20% at release or over the drug product shelf-life for [redacted] In order to support the proposed limit of [redacted] you will need to conduct an embryo-fetal development study in at least one species, either in the mouse or another species using a drug batch containing an appropriate level of [redacted] Clarification: [redacted]	Email Lifecycle	4/11/2008 4/18/2008	Response sent by email, formal response to be submitted in the next lifecycle. Submission Sequence 0010

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b(4)

4/16/2008

22-253

Division of Neurology Products

APPEARS THIS WAY
ON ORIGINAL

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete	As per the table in pg 46 of the Clinical Overview submitted with the original application, total exposure to LCM in ALL clinical studies was 3639 subjects. Please provide information to fill out the following table: Table. Overall exposure to lacosamide and placebo in all studies Formulation/population Total number of unique exposures LCM Placebo Oral formulation (tablet, capsule) Phase 1 – oral only Partial-onset seizures: EP Pool (tablet) Partial-onset seizures: SP586/SP598 (capsule) Diabetic Neuropathic Pain Pool Mixed neuropathic pain Post-herpetic neuralgia Total exposures to oral formulation (tablet, capsule) Solution for infusion Phase 1 iv pool Partial-onset seizures: Phase 2/3 iv pool Total exposures to solution for infusion	Email		Clarification requested on 4/17/08: "Regarding the request for the number of patients actually exposed to placebo, does the DIVISION want the count (and associated subject years of exposure) for subjects who were ever treated with placebo regardless of whether or not they also received LCM (ie, for EP pool oral formulation, this would include subjects who were randomized and received LCM, but also received placebo during the Titration Phase)? This would result in some subjects being counted in both the LCM and Placebo columns of the table requested (and thus would not represent unique exposures). Alternatively, is the DIVISION requesting the count of subjects randomized to receive placebo who actually received placebo?" Response received 4/18/08: "I would like to see the number of patients who were randomized to placebo plus those who were randomized to LCM but received placebo (only) during the initial weeks of the titration phase (before starting LCM)."
		☑	644 1327 13 1566 25 37 3610 86 199 285 781 291	Lifecycle	4/30/2008	Submission Sequence 0011

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
			Total unique exposures 3639 Person-years of exposure (as of 10/16/06) When providing number of patients exposed to placebo include the number of patients actually exposed to placebo during the titration periods as well as those receiving placebo during crossover phase 1 studies.			

4/18/2008

22-253

Division of Neurology Products

Response Complete ☑	Patients #170106 and # 170111 discontinued from study SP757 (IV lacosamide) because of adverse events of "bradycardia" and "ECG QTc interval prolonged", respectively. Please provide copies of all 12-lead ECG and ECG reports (not just the ECG interpretations currently included in the CRFs) for these patients, from studies SP755, SP774 and SP757.	Lifecycle	4/30/2008	Submission Sequence 0011

4/25/2008

22-253

Division of Neurology Products

Response Complete ☐	Attached is an additional request from DNP's clinical team for lacosamide. Like other requests, you may respond via email and follow up with an official submission. Please provide all laboratory results (chemistry, hematology -specifically % eosinophils- and urinalysis) for subject 588/8061, beyond November 11 2000, until normalization.	Email	5/13/2008	Response to be included in the next lifecycle.

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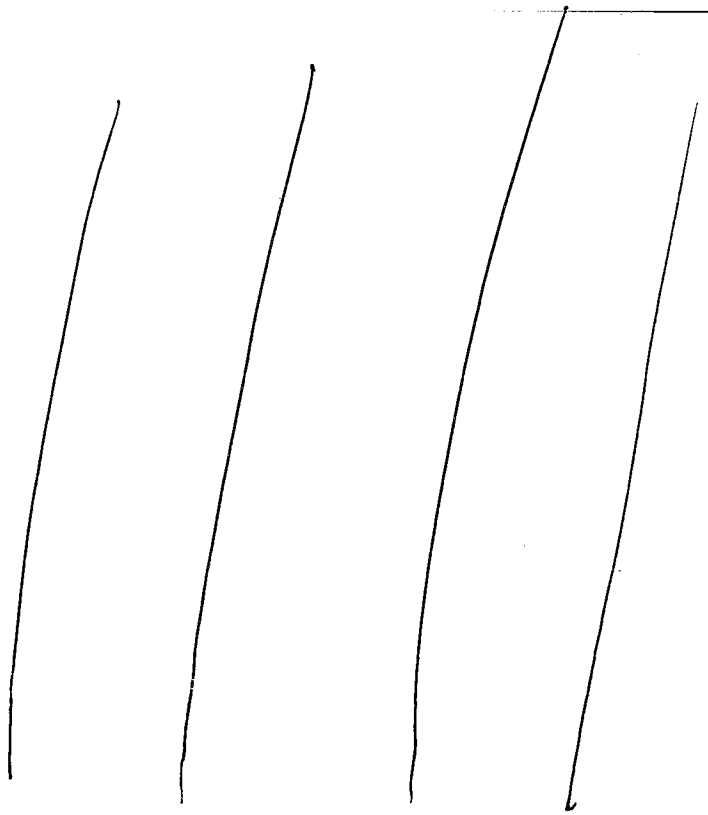
✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response



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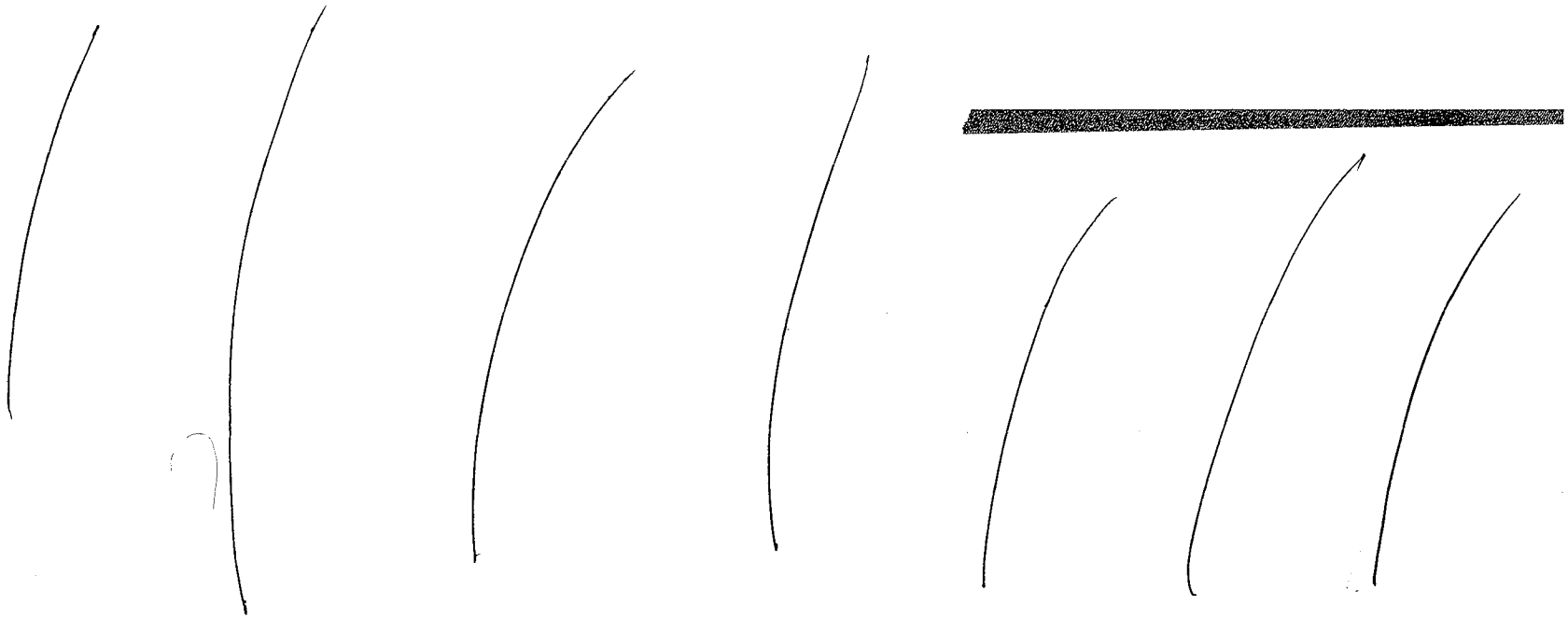
4/29/2008

22-253

Division of Neurology Products

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete	Please provide narratives of patients with the adverse event (MedDRA Preferred Term) "dyskinesia" in all Lacosamide studies. For the patients with epilepsy, include a description of the type and frequency of seizures the patient had at baseline and at the end of the studies. Please send the information no later than Monday, May 5.	Email	4/30/2008	Clarification requested regarding all LCM studies. FDA responded that "all" includes Phase 1 and pain studies. Informed FDA that response will not be available until May 8. If partial responses are available prior to this date, they will be sent.
		☐		Email	5/8/2008	Response and narratives submitted by email. CRF's will be available by 5/15/08. Complete response to be submitted in next lifecycle.



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5/7/2008

22-253

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Division of Neurology Products				
		Response Complete ☐	Please clarify why subject # 754/12512, who attempted suicide during the placebo controlled phase of study 754 while taking LCM 200 mg/day, was not included in your analysis of suicidality.	Email	5/19/2008	Repsonse emailed including revised narrative. Formal response to be included in the next lifecycle.
		Response Complete ☐	The following patients discontinued from the open label epilepsy studies due to either cardiac disorders or ECG investigations. 667010502 667016937 755122402 755108404 Please provide the narratives and CRFs for these patients. If this information has been submitted, direct the reviewer to the exact location in the application. Please also submit the ECGs for Subject 755122303	Email	5/16/2008	Responses submitted by email including requested ECGs and narratives. Formal responses to be included in the next lifecyle.

5/12/2008

22-253

Division of Neurology Products

APPEARS THIS WAY
ON ORIGINAL

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete	May 12, 2008. Request for information for LCM. 1) Please provide the total number of subjects screened and the total number of subjects who did not fulfill eligibility criteria for the placebo-controlled epilepsy studies. Provide the reasons for which these patients failed eligibility criteria. The following format is provided as an example. □ n % Screened□ Entered studies□ Did not fulfill eligibility criteria Concomitant disease Uncontrolled hypertension Elevated LFT Elevated creatinine Etc. Protocol exclusionary medication Antipsychotics Benzodiazepines Etc. Etc. □ 2) Provide a summary table of all baseline concomitant medications in the EP S1, by treatment group (similar to Table 4.1.1, but including all medications, not only medications taken by 10% of patients). 3) Provide a summary table of all baseline concomitant diseases in the EP S1 pool, by treatment group (similar to Table 5.1.1, but including all diseases, not only those presented by 5% of patients). ☐ 4) The intravenous (IV) phase 2/3 epilepsy studies recruited patients from the open label oral tablet studies. Please clarify what were the criteria for selection of patients for the phase 2/3 IV LCM studies. 5) Provide a summary table of all baseline concomitant diseases and concomitant medications taken by patients in the IV phase 2/3 LCM studies.	Email	5/16/2008	Email responses sent for Questions 2,3, and 4 including supporting tables. FDA sent an email on 5/16/08 requesting the following clarification from our partial response: The original request refers to concomitant medications and diseases at baseline before entering the studies. The sponsor's table EP 5.1.1 is entitled:"medications taken during the baseline phase in population pool S1". It is unclear whether this table refers to medications at entry or to medications taken during the placebo-controlled period ("baseline phase") which (would include baseline plus new medications taken during the placebo-controlled period). Similarly, EP 5.1.2 refers to concomitant diseases. Please clarify that these tables refer to the baseline use of medications and diseases. Clarification was submitted to the FDA by email on 5/19/08 and FDA confirmed that clarification was sufficient. Formal responses to be submitted in the next lifecyle. Clarification for Question 5 was emailed on 5/16/08. FDA responded and requested we use scenario 2 for responding. This response will take 2-3 weeks. Question 1 will be submitted by May 30, 2008.

Request Date	*NDA#*	*Division*	*Request*	*Reponse Type*	*Reponse Date*	*Response*
		Response Complete	NDA 22-254 and NDA 22-255 CMC IR #3 Comments for NDA 22-254 (solution for infusion) ☐ 1. The diluent compatibility data indicates an incompatibility between the drug product and the dextrose diluent. The impurity contents associated with RT — and RT — exceed the ICH qualification limit based on your proposed maximum daily dose. Provide justification for the use of the drug product with the dextrose diluent. Include in your justification the identity of the impurities identified by RT — and RT — as well as data demonstrating their safety for use in humans.	Email	5/16/2008	Email response submitted including revised labels. Formal response to be included in the next lifecycle. Quality Overall Summaries to also be included in lifecycle.

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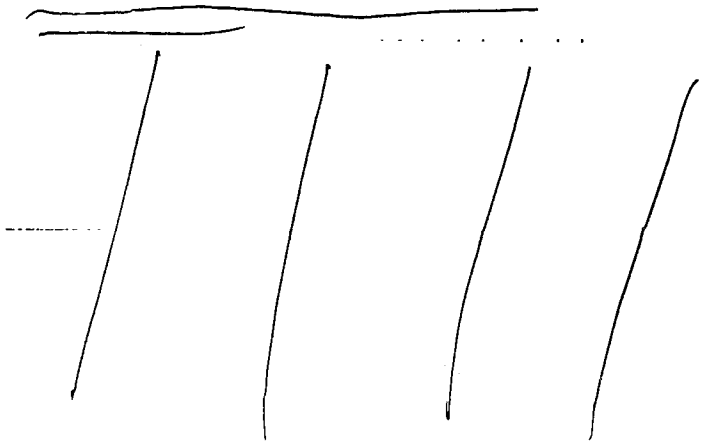

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5/16/2008

22-253

Division of Neurology Products

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete ☐	Question 1 Please comment on the apparent dose response in the treatment emergent use of analgesics (including opiates), anesthetics, psycholeptics, systemic corticosteroids, muscle relaxants, cough and cold preparations, beta blocking agents, calcium channel blockers and agents acting on the renin-angioetensin system in EP S2 (as per Table EP 4.1.4). Question 2 Please comment on whether PR prolongation or adverse cardiac events occurred with concomitant use of beta-blockers or calcium channel blockers with LCM.	Email	5/21/2008	Responses sent by email. Formal responses to be submited in the next lifecycle.

5/20/2008

22-253

Division of Neurology Products

		Response Complete ☐	Please clarify know how the subjects were classified as Poor Metabolizers and Extensive Metabolizers in Study SP643. Provide a summary table (see the example below) indicating which analytical assay validation method was used in which clinical pharmacology and biopharm studies. Validation assay information is not readily available from some of your PK study reports. Table provided in Word format.			Question 1 is being reviewed and is planned on being emailed on May 27th. Question 2 is being worked on by the bioanlytical group and a time line will be provided asap.

5/22/2008

22-253

Division of Neurology Products

		Response Complete ☐	You previously sent laboratory results for subject 588/8061 for several dates including November 13 and December 20, 2000, as well as an AE report that was written in English describing changes in his liver enzymes on November 24, November 28, and December 1, 2000. Results for bilirubin are not included in this narrative for November 24 or for November 28, and there are no units included on the findings for December 1 in the narrative. We are now requesting that you provide copies all of the laboratory reports (including chemsitry with bilirubin) for November 24, November 28, and December 1, 2000.	Email	5/23/2008	Response sent by email. Formal response to be submitted in the next lifecycle.

FDA Outstanding Requests

Request Date	*NDA#*	*Division*	*Request*	*Reponse Type*	*Reponse Date*	*Response*
4/25/2008						
	22-253					
		Division of Neurology Products				
		Response Complete ☐	Attached is an additional request from DNP's clinical team for lacosamide. Like other requests, you may respond via email and follow up with an official submission. Please provide all laboratory results (chemistry, hematology -specifically % eosinophils- and urinalysis) for subject 588/8061, beyond November 11 2000, until normalization.	Email	5/13/2008	Response to be included in the next lifecycle.
4/29/2008						
	22-253					
		Division of Neurology Products				
		Response Complete	Please provide narratives of patients with the adverse event (MedDRA Preferred Term) "dyskinesia" in all Lacosamide studies. For the patients with epilepsy, include a description of the type and frequency of seizures the patient had at baseline and at the end of the studies. Please send the information no later than Monday, May 5.	Email	4/30/2008	Clarification requested regarding all LCM studies. FDA responded that "all" includes Phase 1 and pain studies. Informed FDA that response will not be available until May 8. If partial responses are available prior to this date, they will be sent.
		☐		Email	5/8/2008	Response and narratives submitted by email. CRF's will be available by 5/15/08. Complete response to be submitted in next lifecycle.
5/7/2008						
	22-253					
		Division of Neurology Products				

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete ☐	Please clarify why subject # 754/12512, who attempted suicide during the placebo controlled phase of study 754 while taking LCM 200 mg/day, was not included in your analysis of suicidality.	Email	5/19/2008	Repsonse emailed including revised narrative. Formal response to be included in the next lifecycle.
		Response Complete ☐	The following patients discontinued from the open label epilepsy studies due to either cardiac disorders or ECG investigations. 667010502 667016937 755122402 755108404 Please provide the narratives and CRFs for these patients. If this information has been submitted, direct the reviewer to the exact location in the application. Please also submit the ECGs for Subject 755122303	Email	5/16/2008	Responses submitted by email including requested ECGs and narratives. Formal responses to be included in the next lifecyle.

5/12/2008

22-253

Division of Neurology Products

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Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete	May 12, 2008. Request for information for LCM. 1) Please provide the total number of subjects screened and the total number of subjects who did not fulfill eligibility criteria for the placebo-controlled epilepsy studies. Provide the reasons for which these patients failed eligibility criteria. The following format is provided as an example. n % Screened Entered studies Did not fulfill eligibility criteria Concomitant disease Uncontrolled hypertension Elevated LFT Elevated creatinine Etc. Protocol exclusionary medication Antipsychotics Benzodiazepines Etc. Etc. 2) Provide a summary table of all baseline concomitant medications in the EP S1, by treatment group (similar to Table 4.1.1, but including all medications, not only medications taken by 10% of patients). 3) Provide a summary table of all baseline concomitant diseases in the EP S1 pool, by treatment group (similar to Table 5.1.1, but including all diseases, not only those presented by 5% of patients). ☐ 4) The intravenous (IV) phase 2/3 epilepsy studies recruited patients from the open label oral tablet studies. Please clarify what were the criteria for selection of patients for the phase 2/3 IV LCM studies. 5) Provide a summary table of all baseline concomitant diseases and concomitant medications taken by patients in the IV phase 2/3 LCM studies.	Email	5/16/2008	Email responses sent for Questions 2,3, and 4 including supporting tables. FDA sent an email on 5/16/08 requesting the following clarification from our partial response: The original request refers to concomitant medications and diseases at baseline before entering the studies. The sponsor's table EP 5.1.1 is entitled:"medications taken during the baseline phase in population pool S1". It is unclear whether this table refers to medications at entry or to medications taken during the placebo-controlled period ("baseline phase") which (would include baseline plus new medications taken during the placebo-controlled period). Similarly, EP 5.1.2 refers to concomitant diseases. Please clarify that these tables refer to the baseline use of medications and diseases. Clarification was submitted to the FDA by email on 5/19/08 and FDA confirmed that clarification was sufficient. Formal responses to be submitted in the next lifecyle. Clarification for Question 5 was emailed on 5/16/08. FDA responded and requested we use scenario 2 for responding. This response will take 2-3 weeks. Question 1 will be submitted by May 30, 2008.

Request Date	*NDA#*	*Division*	*Request*	*Reponse Type*	*Reponse Date*	*Response*
		Response Complete	NDA 22-254 [redacted] b(4) CMC IR #3 Comments for NDA 22-254 (solution for infusion) ☐ 1. The diluent compatibility data indicates an incompatibility between the drug product and the dextrose diluent. The impurity contents associated with RT [redacted] and RT [redacted] exceed the ICH qualification limit based on your proposed maximum daily dose. Provide justification for the use of the drug product with the dextrose diluent. Include in your justification the identity of the impurities identified by RT [redacted] and RT [redacted] as well as data demonstrating their safety for use in humans.	Email	5/16/2008	Email response submitted including revised labels. Formal response to be included in the next lifecycle. Quality Overall Summaries to also be included in lifecycle.

b(4)

b(4)

5/16/2008

22-253

Division of Neurology Products

Request Date	NDA#	Division	Request	Reponse Type	Reponse Date	Response
		Response Complete ☐	Question 1 Please comment on the apparent dose response in the treatment emergent use of analgesics (including opiates), anesthetics, psycholeptics, systemic corticosteroids, muscle relaxants, cough and cold preparations, beta blocking agents, calcium channel blockers and agents acting on the renin-angioetensin system in EP S2 (as per Table EP 4.1.4). Question 2 Please comment on whether PR prolongation or adverse cardiac events occurred with concomitant use of beta-blockers or calcium channel blockers with LCM.	Email	5/21/2008	Responses sent by email. Formal responses to be submited in the next lifecycle.

5/20/2008

22-253

Division of Neurology Products

		Response Complete ☐	Please clarify know how the subjects were classified as Poor Metabolizers and Extensive Metabolizers in Study SP643. Provide a summary table (see the example below) indicating which analytical assay validation method was used in which clinical pharmacology and biopharm studies. Validation assay information is not readily available from some of your PK study reports. Table provided in Word format.			Question 1 is being reviewed and is planned on being emailed on May 27th. Question 2 is being worked on by the bioanlytical group and a time line will be provided asap.

5/22/2008

22-253

Division of Neurology Products

		Response Complete ☐	You previously sent laboratory results for subject 588/8061 for several dates including November 13 and December 20, 2000, as well as an AE report that was written in English describing changes in his liver enzymes on November 24, November 28, and December 1, 2000. Results for bilirubin are not included in this narrative for November 24 or for November 28, and there are no units included on the findings for December 1 in the narrative. We are now requesting that you provide copies all of the laboratory reports (including chemsitry with bilirubin) for November 24, November 28, and December 1, 2000.	Email	5/23/2008	Response sent by email. Formal response to be submitted in the next lifecycle.

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Thursday, May 22, 2008 5:00 PM
'Blumberg Alan'; 'DOttavio Misty'
Sullivan, Matthew; Ware, Jacqueline H
Subject: Request for information - Lacosamide NDA

Importance: High

Dear Alan,

Below is a request from the Division's clinical review team for lacosamide. Like other requests, you may respond via email and follow up with an official submission.

- You previously sent laboratory results for subject 588/8061 for several dates including November 13 and December 20, 2000, as well as an AE report that was written in English describing changes in his liver enzymes on November 24, November 28, and December 1, 2000. Results for bilirubin are not included in this narrative for November 24 or for November 28, and there are no units included on the findings for December 1 in the narrative. We are now requesting that you provide copies all of the laboratory reports (including chemsitry with bilirubin) for November 24, November 28, and December 1, 2000.

We request that you submit this information by 10am on May 23, 2008, if possible.

Thanks,
Jackie

****

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Wednesday, May 21, 2008 7:53 AM
'Blumberg Alan'
Cc: Ware, Jacqueline H b(4)
Subject: RE: FDA Request for Information - NDA 22-253, 22-254 [redacted]
Attachments: 52008 PK table.doc

Dear Alan,
Here is a WORD file with the table that was originally included below.
Thanks,
Jackie
****

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

From: Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]
Sent: Wednesday, May 21, 2008 7:25 AM
To: Ware, Jacqueline H
Subject: RE: FDA Request for Information - NDA 22-253, 22-254, [redacted] b(4)

Any chance for sending this as a Word document came in a bit scrambled.

Thanks,
Alan

From: Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]
Sent: Tuesday, May 20, 2008 10:29 PM
To: Blumberg Alan; DOttavio Misty
Cc: Sullivan, Matthew; Ware, Jacqueline H
Subject: FDA Request for Information - NDA 22-253, 22-254, [redacted] b(4)

Dear Alan,

Below are several requests from the clinical pharmacology review team for lacosamide. Like other requests, you may respond via email and follow up with an official submission.

- Please clarify know how the subjects were classified as Poor Metabolizers and Extensive Metabolizers in Study SP643.

- Provide a summary table (see the example below) indicating which analytical assay validation method was used in which clinical pharmacology and biopharm studies. Validation assay information is not readily available from some of your PK study reports.

Brief Description	Study Number	Validation Report No.	Type of Assay	Matrix	Analytes	LOQ
Dose-proportionality						
Single dose-tablets						
Multiple dose-tablets						
Single dose-IV						
	SP835					
	SP587					
	SP836					
	SP588					
	SP 834					
— 0584-haav-hp						
— 0584-haav-hu ka215 LC/MS/MS	b(4)					
Special populations						
Renal Impairment						
Hepatic Impairment						
CYP2C19 EM vs. PM						
Age and gender						
Race						
	SP641					
	SP642					
	SP643					
	SP620					
	SP661					
Drug interaction studies						
Digoxin						

Metformin
Omeprazole
Oral contraceptive
Effect on valproic acid
Valproic acid effect Cabamezapine effect
Effect on cabamezapine

SP644

SP660

SP863

SP599

SP601

SP602

SP603

SP618

Comparative BE

[redacted] b(4)
iv solution vs. tablet
iv solution vs. tablet

[redacted]

SP658

SP645

ikp094-04-05-he
ba583-03
pc27528-1
Plasma, urine
Plasma
Plasma
LCM, M1
LCM, M1
LCM
Food effect-tablet SP600 [redacted] ka215 b(4) Plasma, urine LCM
QT SP640

We request that you submit this information by May 27, 2008, if possible.

Thanks,
Jackie

****

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

APPEARS THIS WAY
ON ORIGINAL

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Tuesday, May 20, 2008 10:29 PM
'Blumberg Alan'; 'DOttavio Misty'
Sullivan, Matthew; Ware, Jacqueline H
Subject: FDA Request for Information - NDA 22-253, 22-254, [redacted] b(4)

Dear Alan,

Below are several requests from the clinical pharmacology review team for lacosamide. Like other requests, you may respond via email and follow up with an official submission.

- Please clarify know how the subjects were classified as Poor Metabolizers and Extensive Metabolizers in Study SP643.
- Provide a summary table (see the example below) indicating which analytical assay validation method was used in which clinical pharmacology and biopharm studies. Validation assay information is not readily available from some of your PK study reports.

Brief Description	Study Number	Validation Report No.	Type of Assay	Matrix	Analytes	L
Dose-proportionality						
Single dose-tablets	SP835 SP587	[redacted] 0584-haav-hp	LC/MS/MS			
Multiple dose-tablets	SP836 SP588	[redacted] 0584-haav-hu [redacted] ka215	b(4)			
Single dose-IV	SP 834					
Special populations						
Renal Impairment	SP641					
Hepatic Impairment	SP642					
CYP2C19 EM vs. PM	SP643					
Age and gender	SP620					
Race	SP661					
Drug interaction studies						
Digoxin	SP644					
Metformin	SP660					
Omeprazole	SP863					
Oral contraceptive	SP599					
Effect on valproic acid	SP601					
Valproic acid effect	SP602					
Cabamezapine effect	SP603					
Effect on cabamezapine	SP618					
Comparative BE						b(4)
[redacted]			b(4)	[redacted]		
iv solution vs. tablet	SP658	ba583-03		Plasma	LCM, M1	
iv solution vs. tablet	SP645	pc27528-1		Plasma	LCM	
Food effect-tablet	SP600	[redacted] ka215		Plasma, urine	LCM	
QT	SP640		b(4)			

We request that you submit this information by May 27, 2008, if possible.

Thanks,
Jackie

****

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
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phone: 301-796-1160
fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

Ware, Jacqueline H

From: CDER DSI Bioequivalence
Sent: Tuesday, May 20, 2008 11:31 AM
Ware, Jacqueline H; Tandon, Veneeta
Viswanathan, CT; Yau, Martin K; O Shaughnessy, Jacqueline A; Kwon, Hyojong
Subject: NDA 22-254 inspection request

We would like to notify you that we plan to conduct remote audits for the —— and German analytical portions of NDA 22-254. The remote audit will not meet the original requested inspection date of May 28, however we will provide you audit results well before the AGD/PDUFA deadline. Our limited resources do not permit on-site inspections within the available timelines. If significant issues arise during the remote audits, we may need to conduct on-site inspections after the PDUFA deadline. b(4)

Michael Skelly

Ware, Jacqueline H

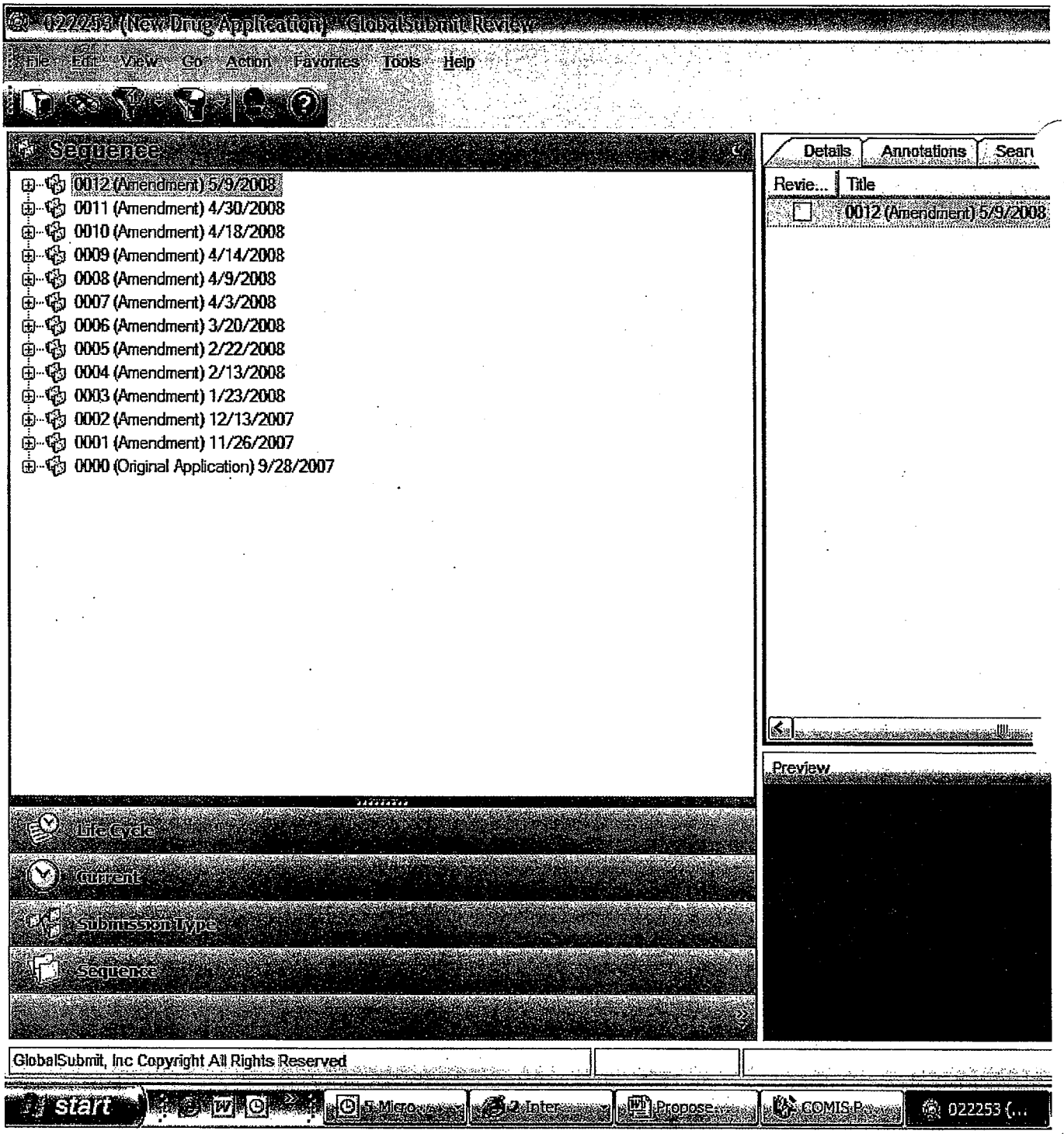
From: Ware, Jacqueline H
Sent: Monday, May 19, 2008 2:50 PM
'Blumberg Alan'; 'DOttavio Misty'
Ware, Jacqueline H; Sullivan, Matthew
Subject: Screenshot of archival submissions to NDA 22-253

Attachments: Picture (Device Independent Bitmap)

Dear Alan,
As we discussed, below is a screen shot of the electronic sequences for NDA 22-253 that DNP reviewers can see using our eCTD review tool (GlobalSubmit Review). Please confirm that this list corresponds on your end to the complete list of archival submissions that Schwarz had made for this application.

Also, would 11am tomorrow (5/20) be an acceptable time for your electronic submission folks to chat with our electronic submission folks about this application?

Thanks,
Jackie



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Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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